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Negative symptoms in schizophrenia are associated with aberrant striato-cortical connectivity in a rewarded perceptual decision-making task

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ABSTRACT

Background: Negative symptoms in schizophrenia have been associated with structural and functional changes in the prefrontal cortex. They often persist after treatment with antipsychotic medication which targets, in particular, the ventral striatum (VS). As schizophrenia has been suggested to arise from dysfunctional connectivity between neural networks, it is possible that residual aberrant striato-cortical connectivity in medicated patients plays a role in enduring negative symptomology. The present study examined the relationship between striato-cortical connectivity and negative symptoms in medicated schizophrenia patients.
Methods: We manipulated motivation in a perceptual decision-making task during functional magnetic resonance imaging. Comparing healthy controls (n = 21) and medicated patients with schizophrenia (n = 18) we investigated how motivation-mediated changes in VS activation affected functional connectivity with the frontal cortex, and how changes in connectivity strength from the neutral to motivated condition related to negative symptom severity.
Results: A pattern of aberrant striato-cortical connectivity was observed in the presence of intact VS, but altered left inferior frontal gyrus (IFG) motivation-mediated activation in patients. The more severe the patient's negative symptoms, the less the connectivity strength between the right VS and left IFG changed from the neutral to the motivated condition. Despite aberrant striato-cortical connectivity and altered recruitment of the left IFG among patients, both patients and healthy controls adopted a more liberal response strategy in the motivated compared to the neutral condition.
Conclusions: The present findings suggest that there is a link between dysfunctional striato-cortical connectivity and negative symptom severity, and offer a possible explanation as to why negative symptoms persist after treatment with antipsychotics.

1. Introduction

Functional magnetic resonance imaging (fMRI) studies have shown that unmedicated patients with schizophrenia (SZ) exhibit reduced activation in the ventral striatum (VS) in response to extrinsic motivation compared to healthy controls (HC) (Juckel et al., 2006b; Nielsen et al., 2012b). It has been suggested that the VS is involved in mediating motivation (Berridge et al., 2009; Knutson et al., 2001) and that dysfunction of the motivation system leads to the symptomology observed in SZ (Barch and Dowd, 2010; Howes and Kapur, 2009; Kapur et al., 2005; Roiser et al., 2009). Both positive (Juckel et al., 2006b; Nielsen et al., 2012b) and negative (Juckel et al., 2006a; Schlagenhauf et al., 2008; Simon et al., 2010; Waltz et al., 2009) symptoms have been associated with abnormal patterns of VS activation. Several studies have reported, however, that motivation-mediated VS activation normalizes after treatment with antipsychotics (Juckel et al., 2006a; Nielsen et al., 2012a) and that the more normal the pattern of activation, the less severe the positive symptoms (Nielsen et al., 2012a). Nevertheless, negative symptoms often persist after treatment with antipsychotics in a sizeable number of patients (Kirkpatrick et al., 2006; Stahl and Buckley, 2007; Tandon et al., 2010).

Negative symptoms are divided into five domains: avolition, anhedonia, asociality and poverty of speech and affect (Kirkpatrick et al., 2006). In patients with schizophrenia these symptoms are associated with poor quality of life (Bow-Thomas et al., 1999; Ho et al., 1998),

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diminished social functioning leading to long-term morbidity (Dickerson et al., 1999; Milev et al., 2005), impaired interpersonal relationships, and generally poor outcome (Milev et al., 2005). There is a relationship between negative symptom severity and reduced gray (Roth et al., 2004; Sigmundsson et al., 2001) and white (Sanfilipo et al., 2000; Wible et al., 2001) matter volume in the frontal cortex. For example, patients rated high in apathy had reduced bilateral frontal cortical volume compared to HC, while those low in apathy did not (Goghari et al., 2010; Roth et al., 2004). Patients high in negative symptoms also had impaired white matter integrity in the inferior frontal gyrus (IFG) (Wolkin et al., 2003) which suggests that negative symptoms may be associated with dysfunctional connectivity.

Several lines of evidence indicate that SZ may arise from dysfunctional connectivity among neural networks (Friston and Frith, 1995; Fusar-Poli et al., 2010; Lynall et al., 2010; Weinberger et al., 1992). Both resting state fMRI and event-related fMRI have revealed aberrant patterns of connectivity within the cortex (Deserno et al., 2012; Wolf et al., 2009; Woodward et al., 2009) and between the cortex and the basal ganglia network which includes the VS (Salvador et al., 2010; Schlagenhauf et al., 2009; Yoon et al., 2013; Zhang et al., 2012). For example, resting state studies have found hyper-connectivity between the prefrontal cortex (PFC) and portions of the bilateral caudate and putamen (Salvador et al., 2010; Zhang et al., 2012). In contrast, an event-related fMRI study examining reward-processing in unmedicated patients found evidence for reduced fronto-striatal functional connectivity (Schlagenhauf et al., 2009). A similar pattern of hypo-connectivity was also observed in medicated patients during a working memory task (Yoon et al., 2013). This suggests that dysfunctional connectivity may endure after treatment with antipsychotics. Despite the suggestion that striato-cortical connectivity is impaired in schizophrenia, how this connectivity changes when performing cognitive tasks has not been thoroughly investigated. In addition, the relationship between impaired striato-cortical connectivity and negative symptom severity in medicated patients has not been fully explored.

Motivation in SZ is thought to be mediated in part by the VS, the target of antipsychotics (Ginovart and Kapur, 2012), yet a deficit of motivation (avolition) is one of the negative symptoms that involves frontal cortex dysfunction (Goghari et al., 2010; Roth et al., 2004) and can persist in medicated patients (Kirkpatrick et al., 2006; Stahl and Buckley, 2007). A manipulation of motivation can, therefore, be used to explore striato-cortical connectivity and its relationship to negative symptoms in SZ. Motivated, healthy participants have increased VS activation that is proportional to reward magnitude (Engelmann and Pessoa, 2007; Knutson et al., 2001; Reckless et al., 2013). Motivation has been shown to alter how individuals bias their decisions (Henriques et al., 1994; Reckless et al., 2013; Reckless et al., 2014), and the left IFG is involved in mediating the change in bias (Mulder et al., 2012).

The aim of the present study was twofold: 1) identify (motivation-mediated) changes in striato-cortical connectivity in medicated patients with schizophrenia during a cognitive task, and 2) examine the relationship between this connectivity and negative symptom severity. A previously used (Reckless et al., 2014) perceptual decision-making task where individuals had to detect a picture of an animal from among non-animal distracters was employed. Motivation was manipulated using financial incentive. In keeping with previous findings (Juckel et al., 2006a; Nielsen et al., 2012a; Reckless et al., 2013; Reckless et al., 2014) it was hypothesized that both HC and medicated patients would have greater VS activation when motivated. Given the hyper-striato-cortical connectivity observed in patients during resting state fMRI studies (Salvador et al., 2010; Zhang et al., 2012), we hypothesized that SZ patients would exhibit aberrant VS–left IFG connectivity compared to HC. As the left IFG has previously been shown to be involved in adjusting response bias (Rahnev et al., 2011; Reckless et al., 2013; Reckless et al., 2014), it was further hypothesized that altered connectivity between this region and the VS would result in patients with SZ failing to adjust response bias from the motivated to the neutral conditions. In view of the relationship between abnormalities in the frontal cortex and negative symptom severity, and the suggestion that connectivity may play a role, we hypothesized that the more abnormal the connectivity, the greater the negative symptom severity.

2. Methods and materials

2.1. Participants

Twenty-two patients with SZ from both in- and outpatient units across four hospitals in Oslo and twenty-two HC were recruited in accordance with local ethics committee guidelines and gave written, informed consent. Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV-TR Axis I disorders (First et al., 2002) and symptom severity was quantified using the Structured Interview for the Positive and Negative Syndrome Scale — SCI-PANSS (Kay et al., 1987). Items were grouped into the consensus driven five-factor model by Wallwork (Wallwork et al., 2012). Functioning was measured using the Global Assessment of Functioning Scale — split version (GAF (Pedersen et al., 2007)). Inter-rater reliability for these instruments has been previously established in our group (Simonsen et al., 2011). Current IQ was assessed using the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2007), which includes matrix reasoning and vocabulary. Individuals were excluded if they had a history of serious head trauma, somatic/neurological illness, drug or alcohol dependence/abuse in the 3 months prior to testing, or a positive urine drug sample on the day of testing. In addition, HC were excluded if they or a first-degree relative had a serious psychiatric illness. Four patients with SZ and one HC exhibited excessive head motion (>3 mm movement between successive scans) during fMRI acquisition and were excluded. The remaining participants were well matched on demographic variables (Table 1). All patients were medicated [atypical: N = 16 (quetiapine n = 8; olanzapine n = 3; aripiprazole n = 2; risperidone n = 2; clozapine n = 1); typical: N = 2 (chlorprothixene n = 1; perphenazine n = 1)]. Medication was standardized using defined daily dose (DDD) (WHO, 2011). At the time of scanning four patients had

Table 1
Participant demographic data.

	Schizophrenia patients (n = 18)	Healthy controls (n = 21)	Statistical test	Significance (2-tailed)
Gender: male/female	13/5	13/8	$\chi^2(1) = 0.46$	0.50
Age, years	29.2 (9.6)	30.0 (6.1)	$t_{(37)} = 0.33$	0.74
Handedness: right/left	15/3	15/6	$\chi^2(1) = 0.77$	0.40
Education, years	13.6 (2.1)	14.0 (2.6)	$t_{(37)} = 0.47$	0.64
WASI IQ	105 (12)	108 (12)	$t_{(36)} = 0.69$	0.49
PANSS				
Positive	10 (4)			
Negative	11 (4)			
Disorganized	5 (1)			
Excited	5 (1)			
Depressed	9 (3)			
Total	56 (13)			
GAF-S	48 (17)			
GAF-F	51 (13)			
Diagnosis: n (%)				
Paranoid	14 (78)			
Schizoaffective	3 (17)			
Residual	1 (6)			
Duration untreated psychosis: weeks, median (range)	12 (1–500)			
Duration of illness: years[a]	8 (6)			
Psychotic episodes[a]	2 (1)			
Defined daily dose (DDD)	1.1 (1)			

Unless otherwise noted scores represent mean (SD).
[a] n = 16

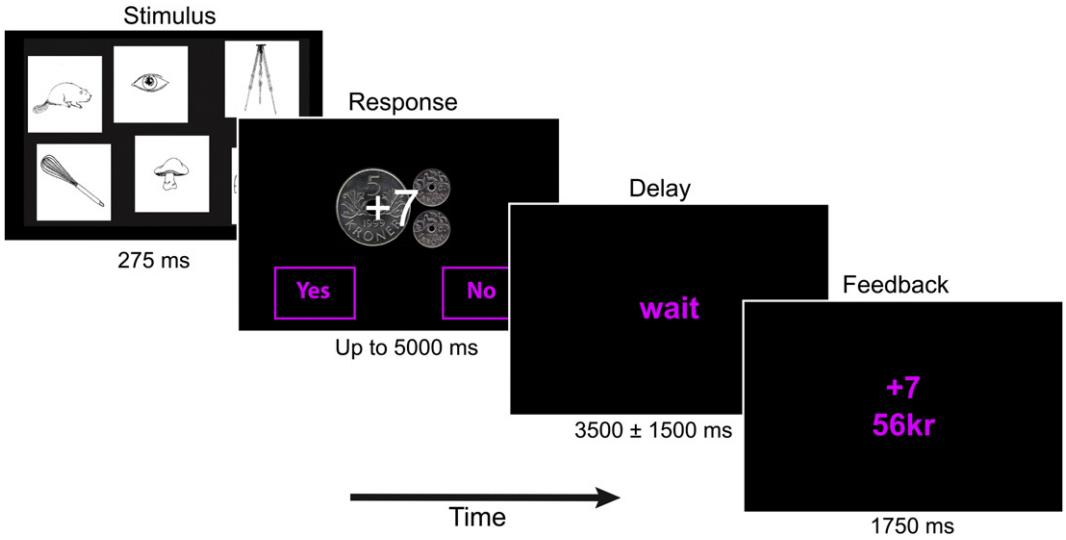

Fig. 1. Experimental task. Participants viewed six black and white drawings for 275 ms. A decision screen indicating the amount of money at stake on that trial immediately followed. A coin with "+7kr" indicated that 7 kroner ($1.25) could be won for correct responses and no money would be lost for incorrect responses. On neutral trials the coin was replaced with a white disk and no money could be won or lost. Participants had up to 5 s to make their response. A delay screen was presented for a jittered duration of 3.5 ± 1.5 s immediately following a decision. Upon termination, a feedback screen depicting the money obtained on that trial and the total amount won up to that point was presented (1.75 s). Trials were separated with a jittered ITI of 5 ± 2 s.

clinically significant delusion (PANSS item P1 ≥ 4); one had clinically significant hallucinations (PANSS item P3 ≥ 4); and five had significant delusions and hallucinations (P1 & P3 ≥ 4). Subjects were paid 300kr ($50) for their participation and kept any additional money they won on the task described below.

2.2. fMRI paradigm

Participants completed two identical sessions of an event-related, perceptual decision-making task consisting of three conditions (motivated, neutral, and baseline) with 36 trials per condition. Each trial was composed of three events: stimulus (275 ms), response (up to 5 s), and feedback (1.75 s) (Fig. 1). In the motivated and neutral conditions six black and white line drawings were briefly presented (*stimulus*) (Snodgrass and Vanderwart, 1980)[1]. Participants then either viewed a screen with a collection of coins with "+7kr" superimposed (motivated condition) or a white circular disk (neutral condition) and used the index finger of one hand to indicate whether one of the six drawings depicted an animal, and the index finger on the other hand if it did not (*decision*). The hand used to indicate that an animal stimulus was present was counterbalanced across participants within each group. Participants could win 7kr ($1.25) for correct responses in the motivated condition. In the neutral condition no money could be won. After a response was made the response screen terminated, a delay of (3.5 ± 1.5 s) occurred and feedback was given (*feedback*). In the motivated condition participants were shown the amount of money won on the trial as well as their cumulative total. Since no money could be won in the neutral condition only the cumulative total was displayed. In the baseline condition participants viewed six right- or left-facing arrows and were told to make a button press with the corresponding hand. The response screen was the same as the neutral condition, and feedback consisted of the word "correct" or "incorrect." Trials from each condition were presented randomly and each trial was separated by a jittered inter-trial interval lasting 5 ± 2 s.

All participants completed a practice version of the task outside of the scanner to limit learning effects. The practice task was identical to the experimental task except that the target stimuli were modes of transportation. Images used in the practice task were not included in the experimental task.

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2.3. Apparatus

The paradigm was programmed and controlled using E-Prime software (version 1.2; Psychology Software Tools, Inc.; Pittsburgh, PA, USA). Stimuli were presented to participants in the scanner using VisualSystem (NordicNeuroLab, Bergen, Norway) and responses were collected using ResponseGrips (NordicNeuroLab, Bergen, Norway).

2.4. Image acquisition

Whole brain, T2*-weighted, echo-planar images (TR = 2 s; TE = 25 ms; FA = 90°) were acquired using a GE Signa HDx 3 T scanner with a standard eight-channel head coil (General Electric Company; Milwaukee, WI, USA). Each volume consisted of 36 slices acquired parallel to the AC−PC plane (sequential acquisition; 3.5 mm thick with a 0.5 mm gap; 260 mm × 260 mm in-plane resolution, 64 × 64 matrix). The first three volumes were discarded to allow for magnetization equilibrium. A T1-weighted FSPGR structural image (TR = 7.7 ms, TE = 3.0 ms, flip angle 12°) was acquired for anatomical comparison. Cushions were placed around the participants' head to minimize movement and earplugs and headphones were used to minimize noise.

2.5. Behavioral analysis

Signal detection theory (Green and Swets, 1966; MacMillan and Creelman, 2009) was used to assess the behavioral response to motivation. Discrimination (d') measures one's ability to identify a target stimulus from a non-target stimulus and is calculated using the inverse z-transformed hit rate (HR) and false positive rate (FPR):

$$d' = Z(\mathrm{HR}) - Z(\mathrm{FPR}).$$

A d' score of 0 indicates an inability to discriminate between stimuli. The better an individual's discrimination, the larger the d' score. Response bias (c) measures a participant's willingness to say that the target stimulus is present and is calculated as:

$$c = -0.5 \times [Z(\mathrm{HR}) + Z(\mathrm{FPR})].$$

A response bias equal to 0 indicates that a participant is equally likely to say that a target or non-target stimulus is present. A larger positive score indicates that the participant is less likely to say that the target stimulus is present (*conservative bias*), while a large negative score indicates an increased willingness to say that the target stimulus is present (*liberal bias*). Given the equal proportion of target and non-target trials

and the neutral payoff matrix in the present study, the mathematically optimal response bias is neutral ($c = 0$).

Three two-way (2 × 2), mixed ANOVAs were used to test the effect of motivation and group on d', c, and response time (RT) (IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). Significant differences were identified at $p < .05$. Effect sizes were calculated using Pearson's r. Values of $r = .10$, .30, and .50 reflect small, medium and large effect sizes respectively (Cohen, 1988).

2.6. fMRI analysis

Data pre-processing and image analysis were conducted using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Trust Centre for Neuroimaging, London, UK). Motion was assessed using the TSDiffANA toolbox (http://sourceforge.net/projects/spmtools/.) All volumes were realigned to the first volume (Friston et al., 1994), and the mean functional and anatomical images were co-registered. The anatomical image was segmented. The functional images were then spatially normalized to Montreal Neurological Institute (MNI) space based on the segmentation parameters, resampled to a voxel size of 3 × 3 × 3 mm, and smoothed using an 8 mm full-width at half-maximum Gaussian kernel. A high-pass-filter using a cut-off value of 128 s and the SPM8 AR1 function were applied.

2.6.1. General linear model

The data were analyzed by modeling the three event types (stimulus, decision, and feedback) as stick functions convolved with a synthetic hemodynamic response function. The six motion parameters estimated during realignment were entered into the model as regressors of no interest. The stimulus and decision events for each condition were contrasted against an implicit baseline at the first-level. These contrast images were moved up to a second-level, random-effects, flexible-factorial model where the main effect of motivation and the interaction between motivation and group were examined. To examine the main effect of group, a separate set of contrast images combining the stimulus and decision events across motivational conditions and comparing them to an implicit baseline were created. These images were then moved up to a second-level, two-sample t-test (HC > SZ; SZ > HC). For whole-brain analyses significant clusters were identified at $p_{FWE} < .05$ (family-wise error corrected). As we had a priori interest in the bilateral VS and left IFG, small-volume correction using regions of interest (ROI) created by Nielsen and Hansen (Nielsen and Hansen, 2004) using probability density estimates from the BrainMap database (Fox and Lancaster, 1994) were applied ($p_{FWE\ (SVC)} < 0.05$). Activations were localized to a particular anatomical region using the SPM anatomy toolbox (Eickhoff et al., 2006; Eickhoff et al., 2007).

2.6.2. Connectivity

Differences in functional connectivity between patients and controls were assessed using the generalized psycho-physiological interaction toolbox (gPPI; https://www.nitrc.org/projects/gppi) (McLaren et al., 2012). As we had a priori interest in how connectivity with the VS changed, two analyses – one using the right and the other using the left VS as the seed region – were performed. For each participant, the toolbox created a design matrix with three sets of columns per run: (1) task regressors — formed by convolving the task events with the canonical hemodynamic response function; (2) BOLD signal observed in the seed region; and (3) PPI regressors for each event — formed by separately multiplying the events by the deconvolved BOLD signal observed in the seed region, and then convolved with the canonical hemodynamic response function. PPI contrast images (motivation > neutral) were created for each individual and represent the differences in functional connectivity with the ventral striatum between the motivation and neutral conditions. To test for group differences in functional connectivity between the VS and the rest of the brain, the contrasts were entered into a second-level, two-sample t-test (SZ > HC; HC > SZ). As with the GLM analysis, significant clusters were identified at $p_{FWE} < .05$, and as we had particular interest in VS connectivity with the left IFG, small-volume correction was applied ($p_{FWE\ (SVC)} < 0.05$).

2.6.3. Post hoc

Partial correlations (Spearman's rho r_s), controlling for the effect of medication were used to examine the relationship between the degree of change in functional connectivity between motivation conditions and positive and negative symptom severity in the SZ group. The mean beta value across the left IFG ROI in the PPI contrast image (which indexes functional connectivity strength with the right VS) was extracted for each participant (Brett et al., 2002) and correlated with the PANSS positive and negative subscale scores.

3. Results

3.1. Behavioral

There was a main effect of motivation on both response bias (c) [$F_{(1,37)} = 8.78$, $p = 0.005$, $r = 0.44$] and response time (RT) [$F_{(1,37)} = 4.54$, $p = 0.04$, $r = 0.33$] with individuals using a more liberal response bias [0.20 (0.54) vs. 0.41 (0.52)] and responding slower [1344 (492) vs. 1263 (372)] in the motivated compared to the neutral condition (Fig. 2 A&B). Motivation did not affect discrimination (d') [$F_{(1,37)} = 0.02$, $p = 0.90$] (Fig. 2C). There was no effect of group on c [$F_{(1,37)} = 0.00$, $p = 0.99$]; RT [$F_{(1,37)} = 0.98$, $p = 0.33$] or d' [$F_{(1,37)} = 0.11$, $p = 0.74$]. There was also no interaction between group and motivation d' [$F_{(1,37)} = 0.20$, $p = 0.66$]; c [$F_{(1,37)} = 0.06$, $p = 0.82$]; and RT [$F_{(1,37)} = 1.57$, $p = 0.22$] (Table 2).

3.2. Imaging

3.2.1. GLM

Whole-brain analyses found significantly greater activation in the bilateral IFG, the right fusiform gyrus and sensory motor area, and in the left substantia nigra in the motivated compared to the neutral condition (motivated > neutral) (Table 3). ROI analysis found additional activation in the bilateral VS (Table 3). There were no group differences in activation (HC > SZ; SZ > HC) for either whole-brain or ROI analyses. There was a significant group by motivation interaction in the left IFG [(−30 41 4, z = 3.09, $p_{FWE\ (SVC)} = 0.039$]. Patients with SZ displayed reduced left IFG activity from the neutral to the motivated condition while HCs showed an increase (Fig. 3).

3.2.2. Connectivity

Compared to patients with SZ, controls showed significantly increased left IFG connectivity to the right VS (r.VS–l.IFG) in the motivated compared to the neutral condition [−30 32–14, z = 3.06, $p_{FWE\ (SVC)} = 0.038$] (Fig. 4). The same pattern was observed between the left VS and left IFG at a trend-wise level [−27 32–14, z = 2.69, $p_{FWE\ (SVC)} = 0.086$].

3.2.3. Correlation between aberrant connectivity and symptomology

The greater the patient's negative symptom sub-score on the PANSS, the less r.VS–l.IFG connectivity increased from the neutral to the motivated condition ($r_s = -0.53$, $p = 0.02$) (Fig. 5). There was no relationship between connectivity and the positive symptom sub-score ($r_s = -0.24$, $p = 0.36$).

4. Discussion

We observed that medicated patients with SZ had an aberrant pattern of connectivity between the right VS and the left IFG. Further, the higher the patient's negative symptom score, the less r.VS–l.IFG connectivity strength changed from the neutral to the motivated condition. This aberrant pattern of connectivity was observed in the presence of a normal VS but altered left IFG response to motivation. Despite both

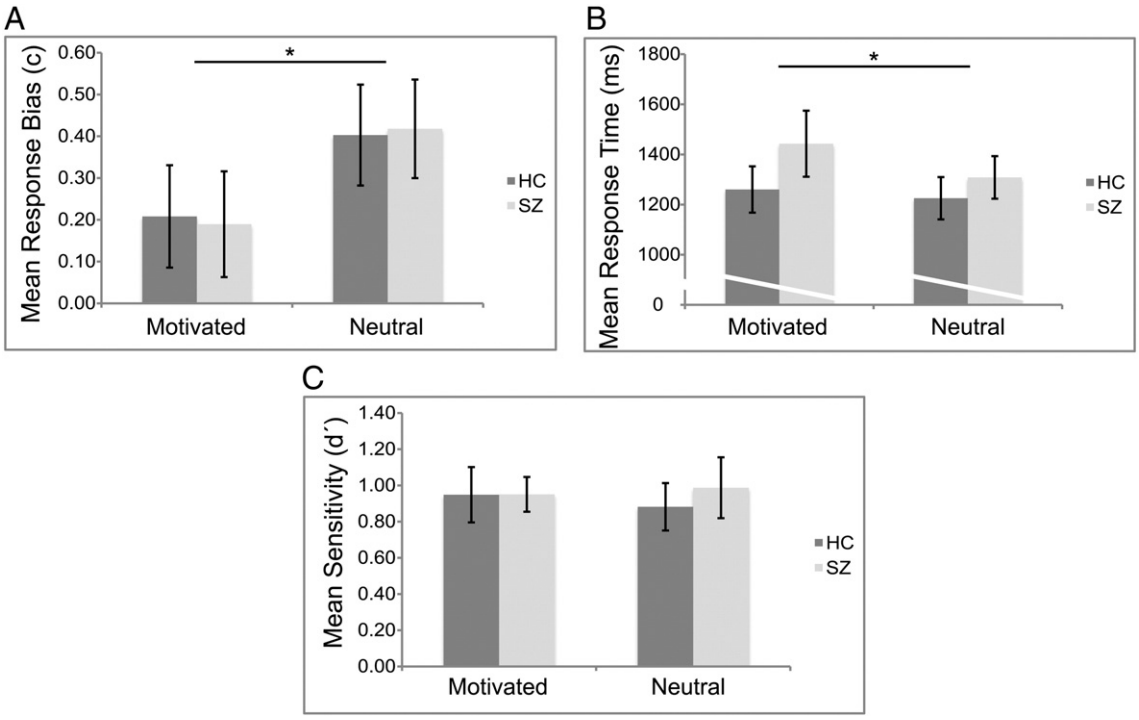

Fig. 2. Effect of motivation on perceptual decision-making behavior. Motivation significantly affected response bias (A) and response time (B). Participants responded slower and were more likely to indicate that the target stimulus was present in the motivated condition compared to the neutral condition. There was no effect of motivation on detection sensitivity (C). Error bars represent standard error. The horizontal line above the bars denotes a significant difference between conditions.

the aberrant left IFG response and r.VS–l.IFG connectivity, there were no behavioral differences between the SZ and HC groups.

It has previously been demonstrated that increased motivation results in increased VS activation (Jensen et al., 2003; Knutson et al., 2001; Reckless et al., 2013). The present study replicated this finding with both the SZ and HC groups showing an increased VS response in the motivated compared to neutral condition. That there was no difference between the two groups is in line with previous findings that have demonstrated that medicated patients with SZ have a normalized motivation-mediated VS response compared to unmedicated patients (Juckel et al., 2006a; Nielsen et al., 2012a). Despite the normalized VS response in the SZ group, a motivation by group interaction was observed in the left IFG. The SZ group exhibited reduced activation from the neutral to the motivated condition while the HC group showed an increase in activation. This pattern of activation has previously been observed in another region of the brain, the VS, in a study investigating motivated learning in medicated patients (Jensen et al., 2008). This suggests that the interaction between motivation and group may not be limited to the left IFG. That medicated patients with SZ continue to exhibit prefrontal cortical dysfunction is in accordance with the literature (Tan et al., 2006; Thormodsen et al., 2011; Walter et al., 2003) and suggests that functional abnormalities remain after antipsychotic treatment.

The abnormal response in the left IFG may be the result of aberrant connectivity with the VS. The HC group had significantly increased connectivity between these two regions from the neutral to the motivated condition while the SZ group did not. The lack of a difference may be the result of abnormally high r.VS–l.IFG connectivity in the neutral condition. This pattern would be in keeping with resting state fMRI studies that have observed hyper-connectivity between cortical and sub-cortical regions (Salvador et al., 2010; Zhang et al., 2012). A similar pattern of aberrant VS–IFG connectivity was observed by Diaconescu and colleagues (Diaconescu et al., 2011) in a learning task. Here medicated patients with SZ had greater VS–IFG connectivity to a cue that did not signal reward than to a cue that did, while healthy controls had the opposite connectivity pattern.

The aberrant striato-cortical connectivity observed in the SZ group suggests that while the motivation-mediated VS response is intact, there is a failure of this response to translate into a connectivity change with fronto-cortical regions. This may be because striato-cortical connectivity is abnormally high during neutral or unimportant events as observed both in Diaconescu and colleagues' learning paradigm (Diaconescu et al., 2011) as well as in resting state studies (Salvador et al., 2010; Zhang et al., 2012).

Table 2
Behavioral measures.

		Schizophrenia patients	Healthy controls
Response bias (*c*)	Motivation	0.19 (0.54)	0.21 (0.56)
	Neutral	0.42 (0.50)	0.40 (0.55)
Sensitivity (*d′*)	Motivation	0.95 (0.41)	0.95 (0.70)
	Neutral	0.99 (0.71)	0.88 (0.60)
Response time (ms)	Motivation	1442 (559)	1260 (423)
	Neutral	1308 (360)	1225 (386)

Scores represent mean (standard deviation).

Table 3
Main effect of motivation.

	Region	Laterality	x	y	z	Peak z-score	p_{FWE}
Whole-brain	Fusiform gyrus	Right	27	−88	−20	7.27	<0.001
	Substantia nigra	Left	−9	−16	−14	6.73	<0.001
	Inferior frontal gyrus (p. orbitalis)	Right	30	29	−26	5.63	<0.001
		Left	−27	23	−23	5.58	<0.001
	SMA	Right	6	14	61	5.39	<0.005
ROI	Ventral striatum	Left	−12	11	−17	5.38	<0.001
		Right	12	14	−14	5.37	<0.001

Whole brain results were thresholded at p_{FWE} (family-wise error corrected) <0.05, $k = 10$. Region of interest (ROI) data are small volume corrected. Only clusters with >10 voxels are reported. Anatomical region, hemisphere and coordinates are based on the Montreal Neurological Institute (MNI) labeling system.

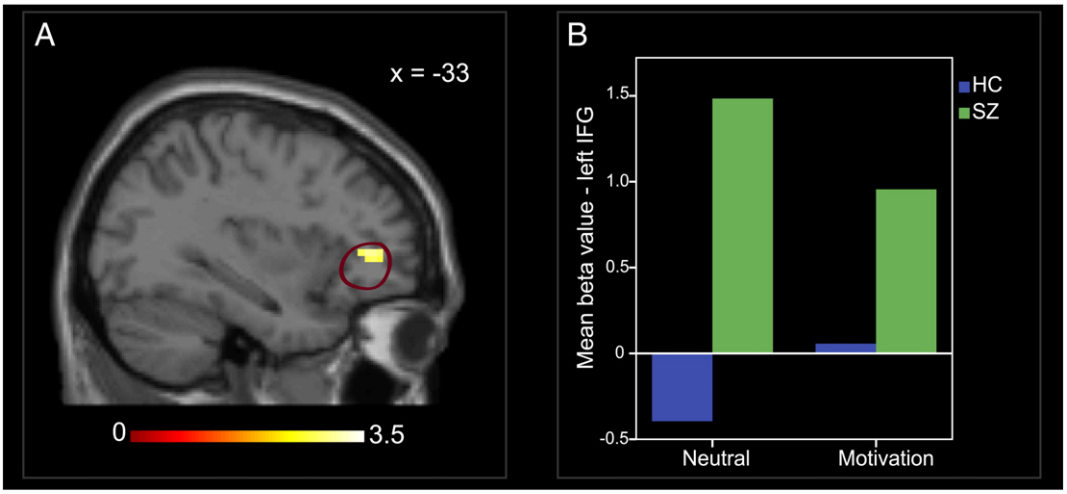

Fig. 3. Group × motivation interaction in the left IFG. A significant group by motivation interaction was observed in the left IFG [(−30 41 4 z = 3.09, $p_{FWE\ (SVC)} = 0.039$] (A). A plot of the mean beta values from across the left IFG ROI (B) revealed that while patients with SZ had reduced activation from the neutral to the motivated condition, HCs showed an increase. The red outline represents the extent of the ROI. IFG = inferior frontal gyrus; ROI = region of interest.

Despite the aberrant pattern of left IFG activation and r.VS–l.IFG connectivity in the SZ group between the motivated and neutral conditions, there was no corresponding behavioral effect. Motivation has previously been shown to result in a more liberal response bias (Henriques et al., 1994; Reckless et al., 2013), and it has been suggested that the left IFG is involved in the change in bias (Rahnev et al., 2011; Reckless et al., 2013; Reckless et al., 2014). We, therefore, speculated that abnormal connectivity between the VS and left IFG in the SZ group would result in failure to adopt a more liberal bias in the motivated condition. However, both the HC and SZ groups adopted a more liberal response bias and responded slower in the motivated compared to the neutral condition. Both groups also performed equally well. The absence of a behavioral effect may suggest that behavioral change can still occur in spite of dysfunctional connectivity. For example, Silverstein and colleagues (Silverstein et al., 2010) found that although patients with SZ and healthy controls had different patterns of activation while performing a perceptual detection task, the two groups performed equally well and did not differ in their response time.

The present study did, however, find an association between aberrant connectivity and negative symptom severity. The smaller the change in connectivity between the right VS and left IFG, the more severe the negative symptoms. Previous studies have found that there is an association between negative symptom severity and both reduced white-matter volume (Sanfilipo et al., 2000) and white matter integrity (Wolkin et al., 2003) in the IFG. These studies offer a potential structural basis for the aberrant connectivity observed in the present study. The relationship between dysfunctional connectivity and negative symptom severity is not limited to the r.VS–l.IFG connectivity observed in the present study. Another study investigating working memory found an association between negative symptom severity and effective connectivity in a fronto-parietal network (Brodersen et al., 2014). This suggests that while r.VS–l.IFG connectivity may play a role, it is dysfunctional connectivity across several neural networks that contributes to negative symptomology in schizophrenia.

It has been suggested that schizophrenia arises from dysfunctional connectivity between neural networks (Friston and Frith, 1995; Fusar-

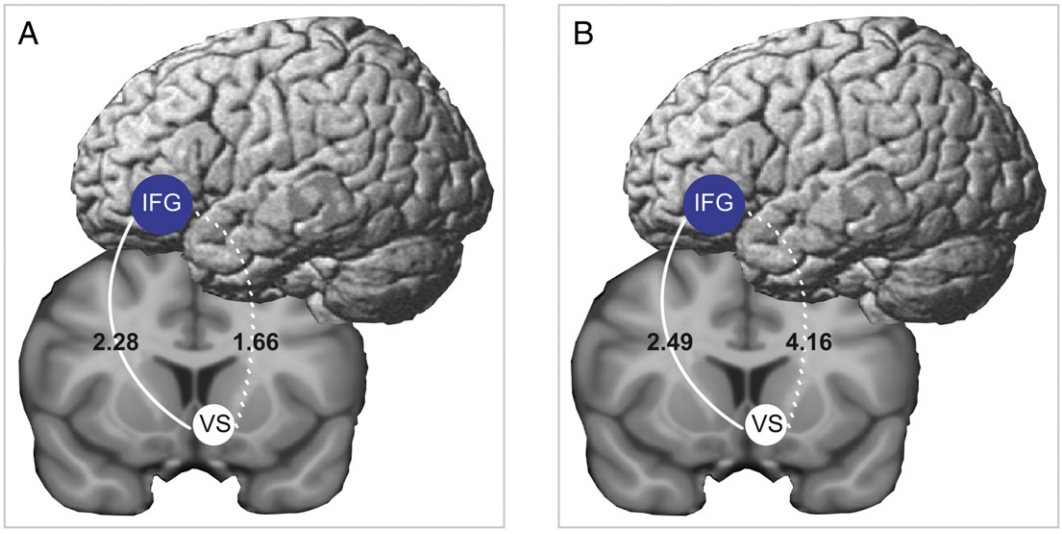

Fig. 4. Effect of motivation on r.VS–l.IFG connectivity. Schematic of the mean connectivity strength between the right VS and left IFG in the motivation (solid line) and neutral (dashed line) conditions for (A) healthy controls and (B) patients with schizophrenia. VS = ventral striatum, IFG = inferior frontal gyrus.

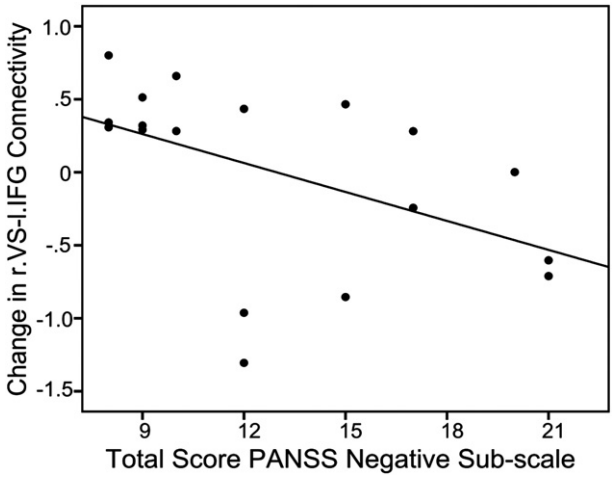

Fig. 5. Relationship between connectivity and symptomology in schizophrenia. A plot of patients' negative symptom sub-score on the PANSS with the difference in r.VS–l.IFG connectivity from the neutral to motivated condition. The more severe the negative symptoms, the less r.VS–l.IFG connectivity changes between the motivation conditions. VS = ventral striatum; IFG = inferior frontal gyrus.

Poli et al., 2010; Lynall et al., 2010; Weinberger et al., 1992). The present study demonstrated that despite a normal VS response to motivation in medicated patients, abnormal striato-cortical connectivity persists and is related to negative symptom severity. The continued presence of aberrant striato-cortical connectivity after treatment with antipsychotics suggests that dysfunctional r.VS–l.IFG connectivity may be one of the mechanisms through which negative symptoms are mediated; however, these findings need replication and further investigation.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary material for this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.04.025.

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